



Contributions to the understanding of osteoarthritis pain

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CONTRIBUTIONS TO THE UNDERSTANDING OF OSTEOARTHRITIS PAIN

**BY
TANJA SCHJØDT JØRGENSEN**

DISSERTATION SUBMITTED 2015



AALBORG UNIVERSITY
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Contributions to the understanding of osteoarthritis pain

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Table of content

Preface	4
Acknowledgement	5
Introduction	6
Aims.....	7
Hypotheses.....	7
Knee osteoarthritis.....	8
Epidemiology.....	8
Aetiology and pathogenesis.....	9
Joint pain.....	10
Joint nociception and sensitisation (from periphery to central manifestations).....	11
<i>Pain pathways</i>	11
<i>Peripheral sensitisation</i>	13
<i>Facilitated central mechanisms</i>	13
Anatomical structures potentially involved in knee OA nociception	14
Current perspectives on knee OA pain	15
Assessment of pain mechanisms in knee pain	17
Manual pressure algometry.....	17
Computer-controlled pressure algometry.....	18
Computerised cuff pressure algometry (Cuff)	18
Explanatory variables	19
<i>Pain intensity</i>	19
<i>Pain distribution</i>	20
<i>Pain description</i>	20
<i>Knee Injury and Osteoarthritis Outcome Score (KOOS)</i>	20
Experimental models of knee pain	21
Changes in pain intensity and sensitivity by injection of local knee joint analgesia	23
Local knee joint analgesia and knee OA	23
Inflammation and knee OA	26
In summary	27

Changes in pain sensitivity and intensity evoked by experimental knee pain	28
Pain intensity.....	28
Pain distribution.....	29
Pain description.....	32
Experimental knee pain and healthy subjects	33
Experimental knee pain and knee OA.....	35
In summary	37
Limitations.....	37
Concluding remarks	38
Perspectives	40
Summary	41
Summary in Danish (Dansk resumé)	43
References.....	45

Preface

The work comprised in this thesis was carried out at the Center for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Denmark, and at the Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen F, Denmark, in the period 2009-2013. The studies were performed under the supervision of Professor, DMSc *Thomas Graven-Nielsen* (main supervisor), Center for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Faculty of Medicine, Aalborg University; Professor, MD, DMSc *Henning Bliddal* (clinical project supervisor), and Senior Researcher, PT, PhD *Marius Henriksen* (project supervisor), both the Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg. The thesis is based on the three papers listed below, which are referred to in roman numerals in the text. The manuscripts are enclosed as Appendix A.

Study I

Joergensen TS, Henriksen M, Danneskiold-Samsoe B, Bliddal H, Graven-Nielsen T. *Experimental Knee Pain Evoke Spreading Hyperalgesia and Facilitated Temporal Summation of Pain. Pain Med* 2013.

Study II

Jorgensen TS, Graven-Nielsen T, Ellegaard K, Danneskiold-Samsoe B, Bliddal H, Henriksen M. *Intra-Articular Analgesia and Steroid Reduce Pain Sensitivity in Knee OA Patients: An Interventional Cohort Study. Pain Res Treat* 2014;2014:710490.

Study III

Jørgensen TS., Henriksen M., Rosager S., Klokke L., Ellegaard K., Danneskiold-Samsøe B., Bliddal H., Graven-Nielsen T. *The Dynamics of the Pain System Is Intact in Patients with Knee Osteoarthritis: An Experimental Study. Submitted to Scan J Pain*, 2014.

*The PhD thesis is submitted to the Faculty of Medicine,
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The making of this PhD thesis has been an interesting, challenging, remarkable and confusing journey with a few bumps on the way. That said, the years spent producing my PhD thesis have been a lot of fun based on outstanding collaboration between the Parker Institute, Copenhagen University Hospital, Bispebjerg and Frederiksberg, and the Center for Sensory-Motor Interaction (SMI) at Aalborg University. A journey like this would have been impossible without the help and support of a number of people, whom I would like to thank.

First I would like to express my gratitude to my supervisor *Professor Thomas Graven-Nielsen* for making me feel at home at the SMI, even though I was living and spending most of my time in Copenhagen. Thank you for always showing great excitement and interest in my studies and for your profitable input. More personally, I will never forget your comforting and wise words at one of our first meetings at SMI: *'Your family is the most important part of your life; if they are happy, you are happy, and I will be happy'*.

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Also Head of the Parker Institute *Professor Henning Bliddal* deserves a special thanks for his undisputable and inspirational wisdom in medical science, which I have benefited from on many occasions. Also, my thank goes to *Professor Bente Danneskiold-Samsøe* for providing me with the opportunity to pursue my goals into the field of medical science.

In spite of some bumps on the way, this journey has without a doubt made me a more knowledgeable, independent, curious and whole person. Thank you *Thomas Graven-Nielsen, Marius Henriksen, Henning Bliddal* and *Bente Danneskiold-Samsøe* for trusting in me and for making the years of my PhD exciting, challenging and an educational experience which I am confident will serve me well in the future.

The research for this thesis would not have been possible without the financial generosity of the Oak Foundation, the SMI and the Danish Agency for Science Technology and Innovation (FI). I also gratefully acknowledge the participation of *my patients and volunteers* for the studies, and the assistance of *staff members* at both the Parker Institute and the SMI.

Finally, my love and deepest admiration and thankfulness go to the most important people of my life, my lovely husband *Peter* and my wonderful children *Asta* and *Carl*. Thank you for bringing out the best in me and for taking my mind off work at home. *Peter*, this would not have been possible without your everlasting support and patience; thank you for trusting and believing in me at all times – *my family means the world to me*.

Tanja Schjødt Jørgensen, september 2014

Introduction

Despite the high prevalence of knee osteoarthritis (OA) it remains one of the most frequent knee disorders without a cure. Pain and disability are prominent clinical features of knee OA [1;2]. The diagnosis is based on clinical presentation supported by radiography. Except for pain, the main features that suggest the diagnosis include stiffness, reduced movement, swelling and crepitus [2]. It is estimated that up to 40% of individuals with radiologic evidence of damage have no pain [3;4] and that there is no clear relationship between the findings of radiologic imaging and sensory symptoms reported by the patients [3;5-7]. The use of more advanced imaging techniques, such as magnetic resonance imaging (MRI), has not clarified the source of pain in OA [8].

A literature review indicates that psychological factors such as depression and anxiety may partially explain the apparent discordance between objective measures and subjective pain reports [9]. However, it is unlikely that such wide variability in population estimates can be attributed to psychological factors alone.

From its nature OA pain is likely to be nociceptive. Nociceptive pain results from noxious stimulation or inflammation/injury of tissue [10]. It is usually localised to the joint with OA, but can also be referred [11]. Hyperalgesia and spontaneous pain in knee OA [12] are most likely related to increased sensitivity of nociceptors located in deep tissue (peripheral sensitisation) and/or to increased responses in dorsal horn or supraspinal neurons (central sensitisation) [1;12-15]. It varies in intensity and is usually worsened by exercise and relieved at rest [11]. It is often episodic but may be constantly present in advanced OA.

The treatment of knee OA is symptomatic and involves alleviating pain, attempting to rectify mechanical malalignment, and identifying and addressing manifestations of joint instability [2;16]. In the short term pharmacologic therapy with intra-articular glucocorticosteroid (steroid)

therapy is long established as having a moderate effect size unlike most OA therapies and is widely used in clinical practice [17]. However, the mechanism of the therapeutic effect in knee OA is unclear [18-20] and whether or not the anti-inflammatory effects of intra-articular glucocorticosteroid have an effect on the increased pain sensitisation in patients with knee OA is unknown.

Aims

In the modern industrialised world musculoskeletal disorders, often in the form of joint pain, constitute a major problem. Nonetheless, some of the mechanisms underlying the pain are unknown. To optimally treat this common disease, an understanding of causes of pain is needed. Especially, knowledge of how joint pain affects the pain systems will provide important new insight and help to explain the basic pain mechanisms in humans. The overarching aim of this thesis is to provide more in-depth knowledge about pain mechanisms in knee OA. More specifically, the aim is to identify the responses to knee pain modulation in healthy subjects and in patients with knee OA, respectively, and to explore how inflammation interacts with the pain system in patients with knee OA.

Hypotheses

The hypotheses of the thesis are:

1. Experimental knee joint pain in healthy subjects evokes local and regional hyperalgesia and the central mechanisms of temporal summation of pain.

2. Local and regional hyperalgesia and temporal summation are related to peripheral nociception in patients with knee OA.
3. Intra-articular anti-inflammation reduces local and regional hyperalgesia and temporal summation of pain.

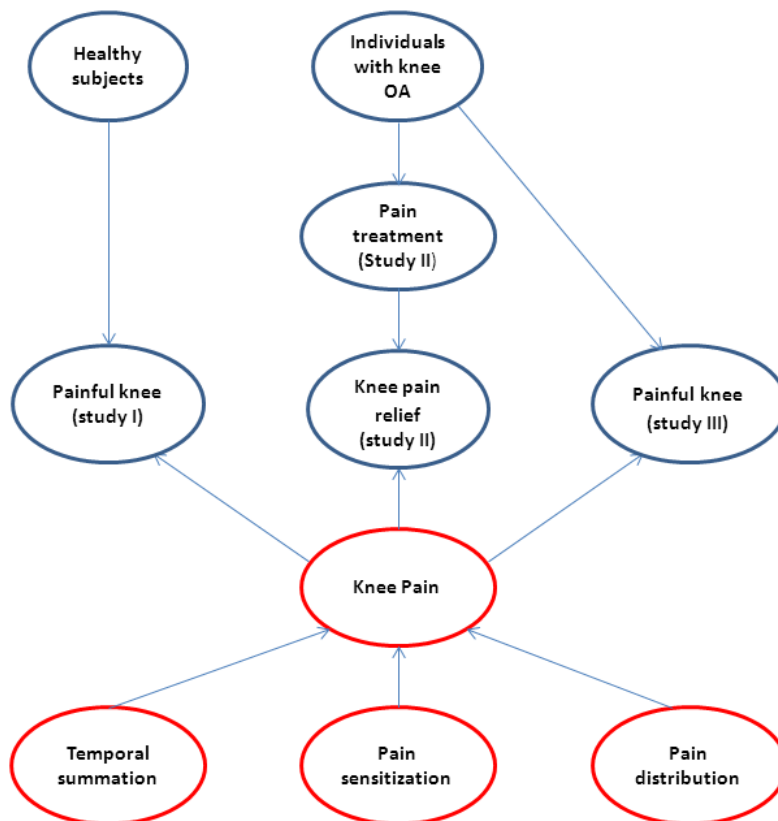


Figure 1 Schematic representation of the PhD project

Knee osteoarthritis

Epidemiology

OA is the most common form of arthritis. It affects growing numbers of people in aging populations and is more common in women than men [16;21;22] and consequently has a significant individual and societal impact [22-24]. The risk of mobility limitations (defined as

needing help to walk or climb stairs) attributable to knee OA alone is greater than those caused by any other medical condition in people aged 65 and over [25;26].

Factors that drive the development of OA include numerous individual factors, such as age, sex, obesity and genetics, as well as joint-specific factors that are likely reflective of abnormal loading of the joints [21;24]

Aetiology and pathogenesis

OA is the clinical and pathological outcome of a range of disorders that result in structural and functional failure of synovial joints [2;27]. Standard objective assessment of pathologic changes in the joint is typically accomplished via radiography, evaluating the presence of osteophytes and joint space narrowing [2;16;28] (Figure 2). Traditionally, it has been considered a disease of articular cartilage, but the current concept holds that OA involves the entire joint organ [16].

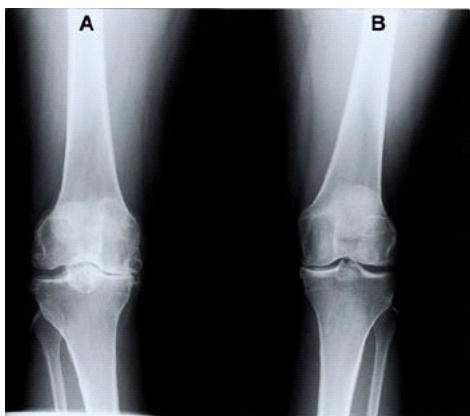


Figure 2 One osteoarthritic knee with medial joint space narrowing confirmed by radiography (A) and a healthy knee (B)

Recently the significance of inflammation and enzymatic cartilage degradation in the pathogenesis of OA has been stressed as important drivers of OA progression [29]. Pathologically, OA is characterised by degradation of type II collagen and cartilage destruction, synovitis, and

bone marrow lesions, and in the long term all tissues of the joint and related structures are affected [29].

Further, it has been suggested that joint pain results from mild inflammation in joint structures such as the synovial layer. Imaging studies have found that painful OA knee joints exhibit more MRI abnormalities than non-painful OA joints. Pathological findings in MRI studies are synovial hypertrophy and synovial effusions as well as subchondral bone marrow oedema [1]. These data and the observation of inflammatory cells in the sublining tissue may provide evidence that OA pain is evoked by recurring inflammatory episodes. At later stages capsular fibrosis and muscle contracture around the joint may contribute to OA pain [30]. Furthermore, whole-knee synovitis assessed by contrast-enhanced MRI has been found to be strongly associated with tibiofemoral radiographic OA and MRI-detected widespread cartilage damage [31]. Also, inflammation in the infrapatellar fat pad is associated with knee OA pain [32].

Despite significant advances in the understanding of the pathology of knee OA, pain pathology associated with knee OA remains largely unknown [33].

Joint pain

Pain has been defined by the International Association of Pain (IASP) as *‘an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damages’* [34]. This definition emphasises the inherent subjectivity of pain, with both sensory and affective dimensions, that is not necessarily associated with tissue damage.

Pain is the most prominent and disabling symptom of OA [1] and a major clinical problem [35]. At a younger age particularly inflammatory diseases, such as rheumatoid arthritis, cause joint pain, whereas elderly people mainly suffer from pain due to OA.

Overall, pain from OA seems to be more frequent than pain from inflammatory joint disease [35]. However, concerning neuronal mechanisms of joint pain much more information is available on inflammatory joint pain. There are a number of reasons for these discrepancies. First, it is presently ill-defined under which conditions OA pain occurs. In most cases OA is a slowly progressing disease, and it is unclear at which stage the joint becomes painful. Second, the pathogenesis of OA pain is unclear [11] and the diagnosis is unspecific reflecting a set of clinical features rather than specific (identified) biological (pathological) processes.

Joint nociception and sensitisation (from periphery to central manifestations)

Pain in arthritis is characterised by hyperalgesia and spontaneous pain (pain at rest). Hyperalgesia means that the application of noxious stimuli causes stronger pain than normal and that pain is even evoked by stimuli whose intensity is normally not sufficient to elicit pain. It is thought that this heightened pain sensitivity results from sensitisation in the nociceptive system [12;36;37].

Pain pathways

Nociception is the neural process involving the transduction and transmission of noxious stimulus to the brain via a pain pathway [38-40]. Nociceptors are the receptors found in most tissues including skin, deep somatic tissues (e.g. muscles and joints) and the viscera [40], which are

activated specifically by noxious stimuli. The 'noxious' information is mediated by primary afferent neurons from the periphery to the central nervous system along axons [39].

Inflammatory substances change the response properties of the nociceptors, activating and sensitising them (peripheral sensitisation) [10;37]. Nociceptors are free nerve endings of nerve fibres [12;37]. There are three fibre types: A β - (group II), A δ - (group III) and C-afferent fibres (group IV). These primary afferent nerve fibres have cell bodies in either the dorsal root ganglia or trigeminal ganglion and terminate in the dorsal horn of the spinal cord. The dorsal horn of the spinal cord is the site where the primary afferent fibres synapse with second-order neurons. It is also the site where complex interactions occur between excitatory and inhibitory inter-neurons and where descending inhibitory tracts from higher centres exert their effect [38-41].

The different fibre types in the joint nerves differ with regard to their mechanosensitivity. Most fibres in the proprioceptive A β -fibre range respond to innocuous movements of the joints, whereas a large number of the nociceptive A δ and C fibers show thresholds in the noxious range (rotation of the joint against the resistance of the tissue and intense local pressure). A large group of mainly C fibres constitute so-called silent nociceptors, because they do not even respond to noxious mechanical stimuli of the normal joint. They respond to mechanical stimulation during inflammation of the joint [11]. These neuronal changes represent a plausible explanation for the occurrence of mechanical hyperalgesia or pain in the inflamed joint [10;11].

Individual differences in transmission and modulation of nociceptive information by the peripheral and central nervous system are one factor that may contribute to OA symptoms. Historically OA has been considered a peripheral disease (i.e., nociceptive damage at the knee) [42]; however, central mechanisms that modulate pain contribute importantly to OA symptomatology [43]. The influence of these central mechanisms can be observed by assessing

perceptual responses to quantifiable noxious stimuli at the knee (primary hyperalgesia) and in areas remote to the knee (secondary hyperalgesia).

Peripheral sensitisation

Tissue injury is followed by a cascade of events involving primary sensory afferents, sympathetic efferents, white blood cells and platelets that induce peripheral sensitisation [39]. Peripheral sensitisation is induced within the first hours after onset of inflammation and can persist over weeks [12].

During inflammation joint nociceptive spinal cord neurons (primary afferent neurons) with joint input are substantially sensitised for mechanical stimuli applied to the joint [11;12;36]. The consequence of these processes is that, under inflammatory conditions, the nociceptive system develops a state of hyperexcitability consisting of enhanced responses to mechanical stimulation of the joint (in the innocuous and noxious range), thereby lowering the excitation threshold in high-threshold neurons. Furthermore, the neurons begin to show increased responses to stimuli applied to regions adjacent to and remote from the joint, and the total receptive field can exhibit enlargement. These changes underlie primary hyperalgesia and secondary hyperalgesia [11;29;36].

Facilitated central mechanisms

Damage of peripheral tissue and injury to nerves typically cause persistent pain and hyperalgesia. Recent evidence indicates that hyperalgesia depends, in part, on central sensitisation [44]. The term central sensitisation is used to describe the phenomena of wind-up, long-term potentiating and secondary hyperalgesia [39].

During the development of inflammation in the joint, neurons in the spinal cord, with input from the inflamed joint, are rendered hyperexcitable [11;12;45]. Thus, inflammation induces neuroplastic changes in the spinal cord, which alter nociceptive processing and lead to facilitation of spinal neuronal processing of the afferent fibres. This leads to increased sensitivity or reduced thresholds to non-noxious pressure on the inflamed joint [11;13;29] and, with some delay, to the adjacent and non-inflamed tissue; the latter indicating that spinal neurons expand their receptive fields [12;13;29;41;44;45]. The fact that pain and hyperalgesia can spread to areas far from the injured region implies that central changes, as opposed to simple convergence, are involved in the spread of hyperalgesia. Other features of facilitated central mechanisms, where the central integrative mechanisms are up-regulated [13], include facilitated temporal and spatial summation of pain [46].

At least at advanced stages of OA, patients show signs of facilitated central mechanisms. They often report widespread pain beyond the OA joint and exhibit lower pressure pain thresholds in cutaneous and subcutaneous structures of the whole leg [36]. In addition, patients with strong local hyperalgesia at the OA knee joint exhibit higher pain summation scores upon repetitive stimulation of the OA knee. The mechanisms of central sensitisation can be very complex, and central sensitisation during OA in particular has not been extensively studied [36;44;47]. Assessment of facilitated temporal summation of pain might shed light on the role of peripheral and central mechanisms in the sensitisation phenomena.

Anatomical structures potentially involved in knee OA nociception

Of the three compartments that combine to form the knee joint (the lateral tibiofemoral compartment, the medial tibiofemoral compartment and the patellofemoral compartment), the

medial tibiofemoral compartment is the most common site of knee OA [48], presumably reflecting of the distribution of the loading with the majority of the load being placed on this compartment [49].

The articular cartilage in an osteoarthritic knee is thinned, damaged or entirely disbanded. When the knee cartilage has deteriorated, new cartilage may be produced; however, the new cartilage cells may grow in irregular, bumpy patterns rather than in the original smooth form. To compensate for the deteriorated or missing cartilage the bones in the joint may produce small bony growths called osteophytes or bone spurs [42;50-52]. It is important to note that cartilage does not contain nerves; hence, damaged cartilage is not a source of pain in knee OA. Likewise, bone spurs are a normal sign of aging, and the presence of bone spurs alone is not a concern. However, the friction between bones and other resulting abnormalities in the knee may cause discomfort and pain [42;50-52].

All innervated tissues inside and around the knee joint represent potential pain generators in knee OA. In addition, nerves themselves - not only peripheral nerves, but also central nervous system - plays a significant role in pain mechanisms in knee OA [37]. Although the main source of pain in knee OA is intra-articular structures, extra-articular sources are not negligible, especially in older patients with a long history of diffuse pain [53]. These differences in pain characteristics in knee areas should be taken into account when examining the pain sources of knee OA [53].

Current perspectives on knee OA pain

Musculoskeletal pain is typically described by patients as a drilling, tight, radiating and diffuse pain sensation with pain referrals, and it is often accompanied by deep-tissue hyperalgesia or allodynia

[54]. Pain localisation in deep tissue is poor, and it is difficult to differentiate between pain arising from muscles, tendons, ligaments and bones and pain arising from joints and their capsules [55].

Pain is the cardinal symptom of knee OA, and currently this disease cannot be cured. Altered pain sensitivity is most likely related to increased sensitivity of peripheral nociceptors and/or central neurons [1;12-14], and it is well known that inflammatory joint diseases lead to both peripheral and central sensitisation of the nociceptive system [14;45].

Inflammation plays a fundamental role in the pathogenesis of knee OA, and there is growing consensus that knee OA involves low-grade inflammation contributing to structural disease progression and generation and maintenance of pain [56-58]. Synovial inflammation acts as a trigger for several signs and symptoms of OA, including stiffness, effusion and joint swelling, and has profound effects on the nociceptive system where cytokines seem to be a major player in the production of such effects [56;57].

Intra-articular steroid injections have beneficial short-term effects on pain and are widely used in clinical practice [17]. However, factors that predict response are poorly characterised, making it difficult to select the patients for whom treatment is most likely to be successful. Although the mechanism of the therapeutic effect in knee OA is unclear, it is likely to be related to the potent anti-inflammatory effect of steroid. It is unknown whether the anti-inflammatory effects of intra-articular steroid influence the increased pain sensitisation phenomena in patients with knee OA is.

Assessment of pain mechanisms in knee pain

Over the last couple of decades quantitative sensory testing (QST) has emerged as a promising means for monitoring and diagnosing pain processing and its alterations in patients [59;60].

Quantitative pain assessment is performed using different methods typically involving psychophysical testing [13]. The technique is based on the application of defined stimuli to the individual under standardised conditions, subsequently asking the participant to rate the experienced intensity of the stimuli. The use of multiple stimuli with different intensities makes it possible to construct a stimulus-response relationship characterising the state of the participant's pain processing.

Manual pressure algometry

The manual pressure algometry (Figure 3) method yields information about mechanical pressure pain thresholds (PPT), which can be used for quantitative evaluation of subjective pain reactions from different tissue structures [61], as well as information about the adaptive response to tonic pain. Manual algometry has been widely used across several conditions such as OA [62-64], myofascial pain syndrome [65;66], fibromyalgia [67;68] and chronic back pain [69;70]. Clinical studies in knee OA have reported generally acceptable reliability of manual algometry [71-73]. Thus, while manual algometry seemingly has good reliability, it is highly operator dependent, and correct application requires training and thorough instruction of both patient and operator [74].



Figure 3 The manual pressure algometer with stop-button and calibration weights.

Computer-controlled pressure algometry

The variability associated with manually-applied pressure stimulation can be minimised through the use of computer-controlled pressure stimulation (Figure 4). It is an easy method which also allows for the measurement of stimulus-response functions that relate the pressure intensity to the pain response [75;76]. In response to a sequence of somatosensory stimuli with the same intensity, the progressive increase in pain perception is defined as the temporal summation of pain, which mimics the initial phase of the wind-up process [13;77]. Appropriate conditions for the assessment of temporal summation are sufficiently short intervals between repeated stimuli of constant strength (such as 10 stimuli at 1 s inter-stimulus intervals) [64;77-79]. This procedure was used in the present thesis. In line with manual algometry this method has been used across several conditions such as fibromyalgia [80;81], OA [82], and healthy subjects [83;84].

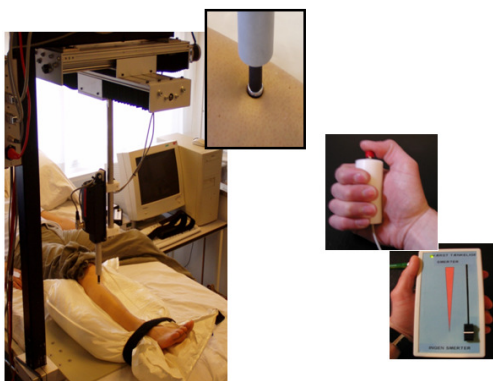


Figure 4 The computerized controlled pressure algometer, including compressor and control panel, a stop-button, and a visual analogue scale.

Computerised cuff pressure algometry (Cuff)

Cuff algometry methodology has been used for quantifying pain sensitivity in the lower legs and arms (Figure 5). Assessments of pressure pain sensitivity include determination of pressure pain thresholds and spatial and temporal summation of pain [85-87]. The cuff algometer will activate a

larger volume of the deep somatic tissue than manual and computer-controlled pressure pain algometers and is less influenced by local pain sensitivity variations.



Figure 5 The computerised cuff pressure algometer, including compressor and control panel, inflatable cuff, and a stop-button with integrated visual analogue scale.

Explanatory variables

Besides those variables acquired in the above-mentioned pain sensitivity methods (PPT and temporal summation), profiling widespread pain in clinical studies requires detailed descriptions of the habitual pain distribution, quality and intensity; valuable tools for achieving this include scales, pain drawings and questionnaires. This thesis includes several measures considered to be of important explanatory value in the analysis of the effect of pain modulation on pain sensitivity.

Pain intensity

For the evaluation of knee OA pain, visual analogue scale (VAS) and numerical rating scale (NRS) assessments of pain intensity are the most common – a single question about the presence of ‘pain, aching or stiffness in or around the knee’ over a specified period of time [21], which has been validated as an appropriate pain instrument for OA [88]. In the present thesis a single

question about the presence of 'pain' in different situations of pain modulation was used, defined as current knee pain in which '0 cm' represents no pain and '10 cm' represents maximal pain.

Pain distribution

The distribution of pain was drawn on an anatomical map. Knee pain was defined as local pain.

Pain occurring in thighs, calves, and feet was defined as widespread pain.

Pain description

The quality of the pain was described using both an English [89;90] and a Danish version of the McGill Pain Questionnaire (MPQ) [91] to explore and identify the individual's use of descriptors to characterise the experience of pain modulation. Clinical studies in different populations have used the MPQ [90;91]. The questionnaire has been validated as an appropriate pain instrument for use in OA [88]. The results of the study by Drewes et al. [91], translating the MPQ into a Danish version and making comparisons to studies of patients speaking other languages, allowed us to use the questionnaire in both an English-speaking and a non-English-speaking population.

Knee Injury and Osteoarthritis Outcome Score (KOOS)

The KOOS questionnaire was developed as an instrument for assessing the patient's opinion about their knee and associated problems. KOOS is self-explanatory, can be easily administered and has been used in different populations [82]. Furthermore, it is widely used for research purposes in clinical trials, large-scale databases and registries and it has high test-retest reliability [92].

KOOS consists of five subscales: Pain, Symptoms, Activities of daily living, Sport and recreation function, and Knee-related quality of life. Standardised answer options are given (5 Likert boxes) and each question is scored from 0 to 4. A normalised score (100 indicating best condition and 0 indicating worst condition) is calculated for each subscale [93]. KOOS is a developmental variant of the WOMAC questionnaire, which was intended for assessment of elderly people with primary OA [94].

Experimental models of knee pain

Knee OA is a chronic pain condition, but it is also characterised by other factors (e.g. inactivity and joint degeneration). Experimental models of knee pain in healthy subjects may be advantageous in the investigation of mechanisms of the nociceptive system related to joint pain. In several studies sensitisation of deep-tissue nociceptors has been demonstrated by injection of algescic substances or external nociceptive stimuli inducing hyperalgesia [54;95-99]. In addition, both spreading hyperalgesia and hypoalgesia have been reported to occur in different tissues after experimental pain [96;97]. Few human experimental knee joint pain models exist, among which injection of hypertonic saline into the infrapatellar fat pad [100-105] is adequate for studies of sensory manifestations related to knee pain. The experimental muscle pain technique as a knee OA model may be criticised, as muscle tissue is not the source of primary pain in knee OA [103;106]. Experimental knee pain is an alternative model.

The infrapatellar fat pad is an intra-articular structure, sensitive to mechanical stimulation, and densely innervated by nociceptors [107;108]. Adipose tissue is a metabolically active endocrine organ that can secrete agents associated with the production of pro-inflammatory

cytokines found in synovial fluid in knee OA joints [109]. Thus, adipose tissue may play a central role in the inflammatory processes of OA.

Change in MRI-detected synovitis in the infrapatellar fat pad are associated with changes in knee OA pain [32;110], and the infrapatellar fat pad may be an important structure to consider in the aetiopathogenesis of knee OA and knee OA pain [32;111]. Furthermore, experimental studies have shown that experimental pain in the infrapatellar fat pad elicits changes in motor function similar to those observed among knee OA patients [101;103].

Thus, experimental infrapatellar fat pad pain is presumably a more valid model of knee OA pain than muscle pain models, but it is unknown whether experimental pain in the infrapatellar fat pad leads to peripheral and/or central sensitisation similar to that observed in knee OA patients [64].

Changes in pain intensity and sensitivity by injection of local knee joint analgesia

The management paradigm for pain in OA has changed little over many decades. However, recent studies have shown that long-term use of standard treatments, including acetaminophen and nonsteroidal anti-inflammatory drugs, fails to reduce mean pain levels beyond minimal clinically important thresholds [112;113]. One potential explanation for suboptimal pain control in OA may be a mismatch between the medications used and the underlying pain mechanism(s) [113].

To predict the response of an analgesic and anti-inflammatory treatment it is important to have a better understanding of the pain sensitisation phenomena in patients with knee OA and the possible effects.

Local knee joint analgesia and knee OA

There is growing consensus that knee OA pain involves a low-grade inflammation [56;57], and the mechanism of the therapeutic effect in knee OA is likely to be related to the potent anti-inflammatory effect [17]. There is evidence of short-term benefit of intra-articular anesthetic injections [114] or of intra-articular glucocorticosteroid injections with pain relief for up to 4 weeks [17;115].

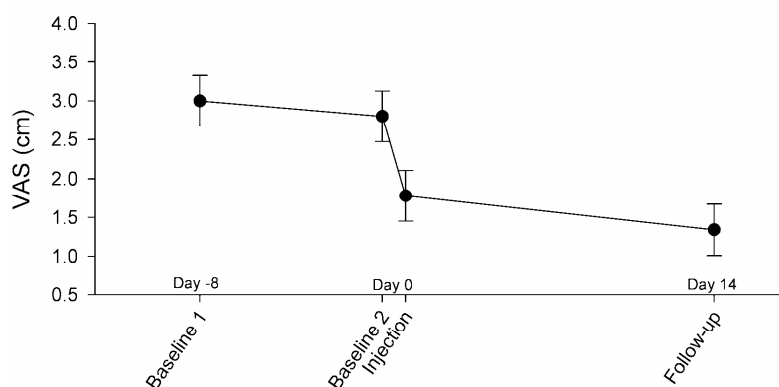


Figure 6 Changes in current knee pain intensity in knee OA patients at baseline, immediately after the intra-articular treatment, and at follow-up (study ii).

Clinical studies have documented inflammation in the synovium and other intra-articular structures of OA knees contributing to the sensitisation of pain [29]. In line with previous observations [17], the results from study (ii) have demonstrated reduced current knee pain intensity immediately after, and two weeks after the intra-articular treatment leading to significantly lower VAS scores (reduced pain intensity) (Figure 6).

Besides the important effects on the patient's reported pain intensity (current knee pain), intra-articular treatment also had important clinical effects on pain sensitivity. In study (ii) the effects of intra-articular treatment have led to immediate higher PPTs (reduced pain sensitivity) at the knee and surrounding muscles (study ii). The effect was sustained for 2 weeks after the injection (Figure 7), supporting the proposed involvement of inflammation in the sensitisation phenomena.

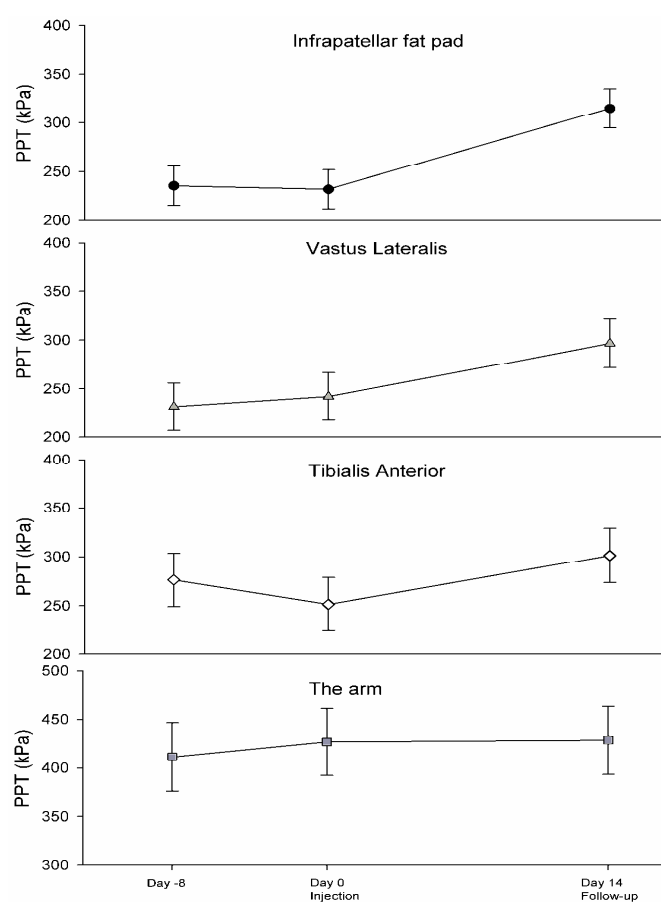


Figure 7 Mean PPTs at the knee (infrapatellar fat pad), the surrounding muscles (vastus lateralis and tibialis anterior), and at the contralateral arm before and two weeks after the intra-articular treatment (study ii).

Clinical pain improvement is influenced by a wide range of parameters, including nociception, psycho-social factors, and affections [116;117]. The lack of association between pain sensitivity (PPT), pain sensitivity changes, and pain improvements in study (ii) could be explained by the difference in the constructs of the pain assessment types; e.g. PPTs are based on instant painful stimulation. This is in contrast with previous findings in which higher pre-operative widespread hypersensitivity may be associated with chronic pain after total knee replacement [118]. Some patients with OA experience pain sensitisation [119], which has the potential to become a risk factor for chronic pain after total knee replacement [120]; however, the patients in the present thesis were not candidates for surgery.

The reduced pain sensitivity observed after the clinical pain relief treatment in study (ii) was not confined to the lower extremity, as a trend towards reduced pain sensitivity was observed at the control site on the contralateral arm. No definitive models explaining the transition from localised to widespread musculoskeletal pain conditions exist, but it has been shown that initial excitation and sensitisation of peripheral nociceptors (e.g. due to joint inflammation) may cause sufficient input to the central pain systems [54;121;122]. The local and widespread effects observed in study (ii) support the notion that input from intra-articular structures may contribute to widespread hyperalgesia and that anti-inflammation may reverse it.

Further, widespread hypersensitivity in mechanical pressure pain and loss of pain modulation in patients with symptomatic knee OA were shown to normalise after knee joint replacement [122]. Also, therapeutic exercise has been shown to yield similar effects on pain sensitivity [82]. The present study (ii) corroborates these findings, indicating that simple analgesia and anti-inflammation reduce widespread hypersensitivity in mechanical pressure pain.

The intra-articular treatment also had a general beneficial effect on self-reported knee related disease impact, as assessed by KOOS [123], although only reaching statistical significance in the symptoms' sub-domain (Figure 8). These results are in line with the meta-analysis by Bellamy et al. [115]

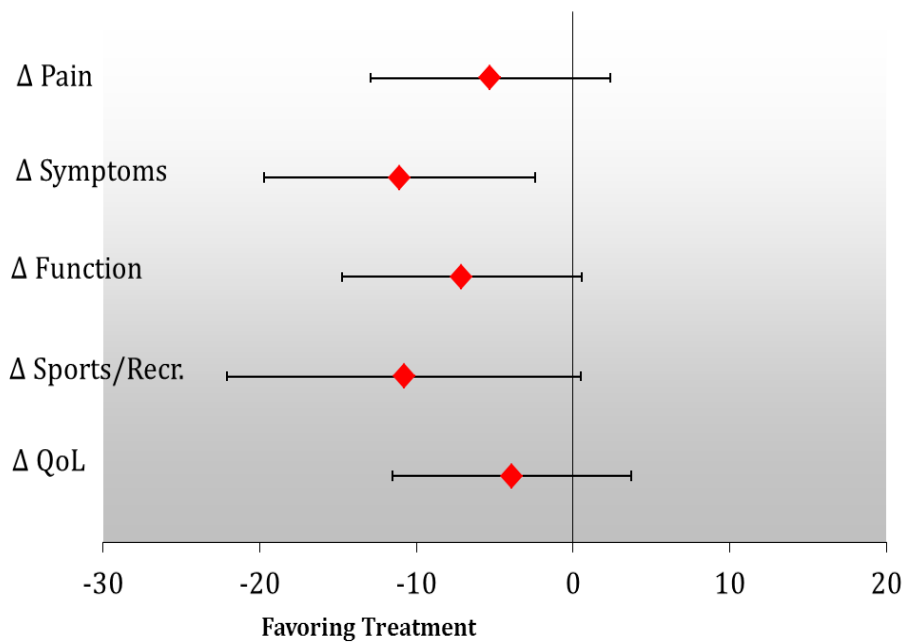


Figure 8 Changes in KOOS questionnaire two weeks after the intra-articular treatment (study ii).

Inflammation and knee OA

It is well known that inflammatory joint diseases lead to both peripheral and central sensitisation of the nociceptive system [14;45;124], and the results from study (ii) may support the proposed involvement of inflammation in the sensitisation phenomena as the effects were sustained for at least 2 weeks at both the knee and the surrounding muscles (Figure 6 & 7).

Synovial inflammation acts as a trigger for several signs and symptoms of OA, including stiffness, effusion and joint swelling [56], and has profound effects on the nociceptive system, where cytokines seem to be a major player in the production of such effects [57]. Clinical studies have shown significant inflammation in the synovium and other intra-articular structures of OA knees, contributing significantly to the sensation of pain [29]. Changes in synovitis in the infrapatellar fat pad were detected by MRI and those changes were associated with changes in knee OA pain [110;125].

In the present thesis clinical pain relief induced by an intra-articular analgesia and anti-inflammatory treatment yielded beneficial effects on both local and widespread hyperalgesia (ii), indicating that inflammation does indeed affect pain sensitivity and seems to play an important role in the pain sensation of the persons with knee OA included in this study.

In summary

Intra-articular analgesia and anti-inflammatory treatment reduced localised and widespread pain sensitivity in patients with knee OA. The effects were immediate and were sustained for at least 2 weeks. Furthermore, this thesis supports the notion that inflammation may play an important role in the sensitisation of the nociceptive system in both joint and soft tissues in knee OA.

Changes in pain sensitivity and intensity evoked by experimental knee pain

The infrapatellar fat pad has been shown to be an active osteoarthritic joint tissue that is able to produce and excrete important inflammatory mediators directly into the knee joint, which might explain the role of the infrapatellar fat pad in the disease process of knee OA [108]. In the study by Hill et al. [110] synovitis was scored at three different locations. MRI-detected change in synovitis was correlated with changes in knee pain. The increase in synovitis was associated with worsening knee pain, and a decrease with less severe pain. These results indicate that the infrapatellar fat pad is a significant source of knee OA pain, suggesting that the treatment of painful OA of the knee should be targeted at synovitis, which may relieve pain.

Experimental pain may not replicate 'real' OA pain although several studies [100;101;103-105] have found that experimental pain induced into the infrapatellar fat pad produced strong knee pain in regions similar to those in patients with knee OA.

Pain intensity

Hypertonic saline caused significantly higher pain intensity compared with isotonic saline in both healthy subject (i) and in knee OA patients (iii) (Figure 9), supporting observations previously reported in healthy subjects.

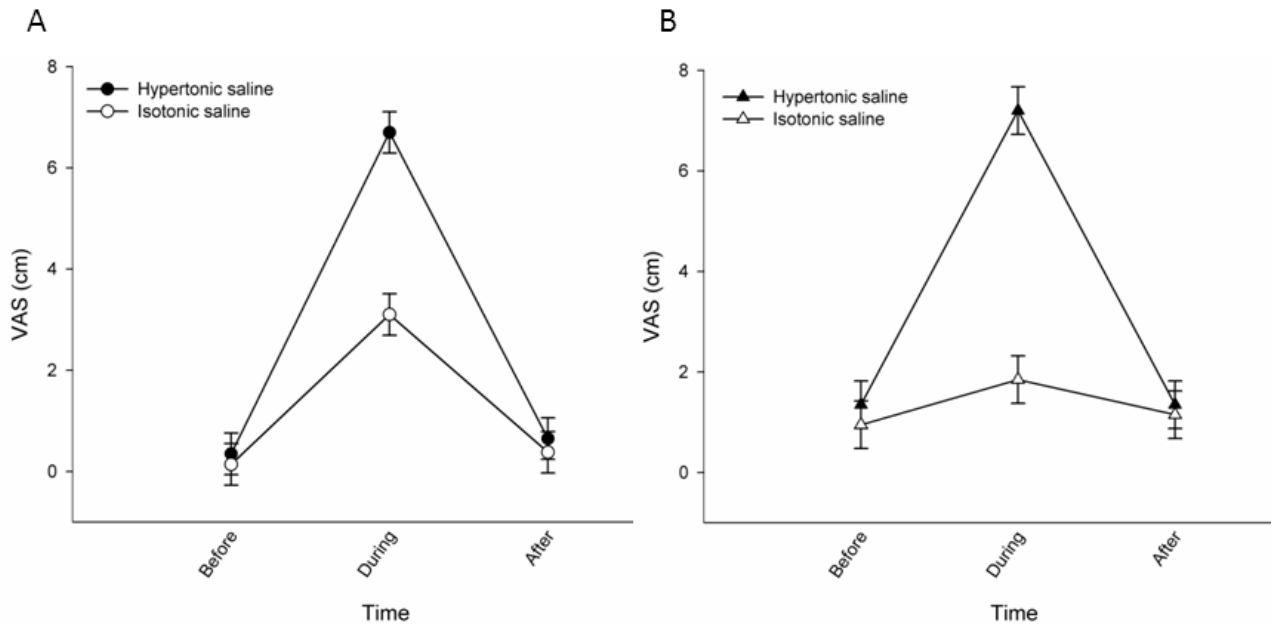


Figure 9 Current knee VAS pain after injection of hypertonic saline in healthy subjects (A; study i) and patients with knee OA (B; study iii) and isotonic saline as control. In both figure A and B there were significant differences between hypertonic and isotonic saline.

Several studies have found that, in healthy subjects, experimental pain induced into the infrapatellar fat pad produced intense knee pain in regions similar to those in patients with knee OA [100;101;103-105;126], indicating that the experimental model behaves similarly in healthy subjects and in patients with knee OA.

Pain distribution

This is the first time experimental pain has been induced in the infrapatellar fat pad in individuals with knee OA (iii). In previous studies on healthy subjects experimental pain was described as local pain in the region medial to the patellar tendon around the injection site [13;64;100]. Study (i) corroborates these findings, although the subjects also reported central and lateral pain as well as referred thigh pain.

The individuals with knee OA described the experimental pain areas as being larger compared with their habitual OA knee pain (Figure 10) as well as having referred pain to the thigh and lower leg, which is in contrast to studies using the experimental pain model in healthy subjects; here the experimental pain areas are smaller [13;64;100;126]. The larger areas may indicate that the patients with knee OA have a facilitation of mechanisms linked with referred pain as suggested previously [13;62;127].

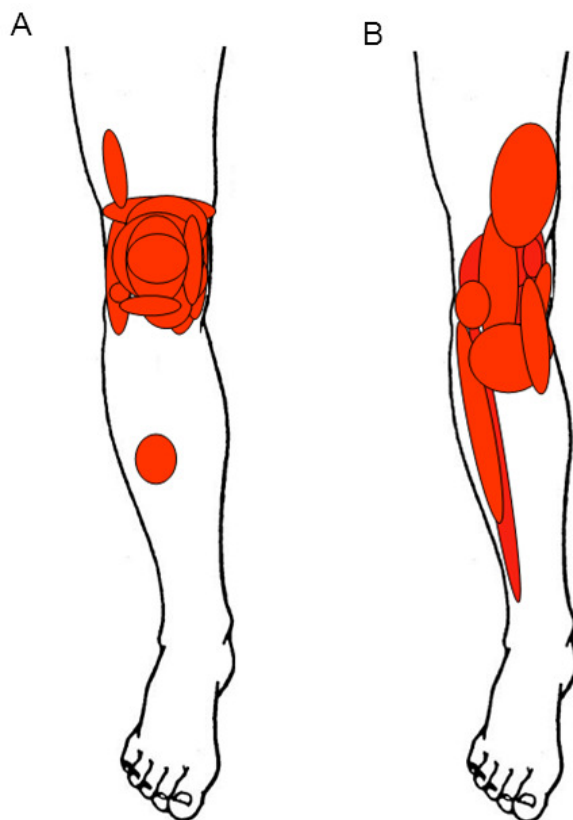


Figure 10 Illustrating pain distributions before (A) and after injection of hypertonic saline (B) in patients with knee OA (study iii).

The pain areas described by the individuals with knee OA in study (iii) were comparable to the pattern described by the healthy subjects in study (i) and in line with similar experimental knee pain models in healthy subjects [100-102;126], although to a greater extent (Figure 11). This could indicate that individuals with knee OA are sensitised, even after anti-inflammatory treatment.

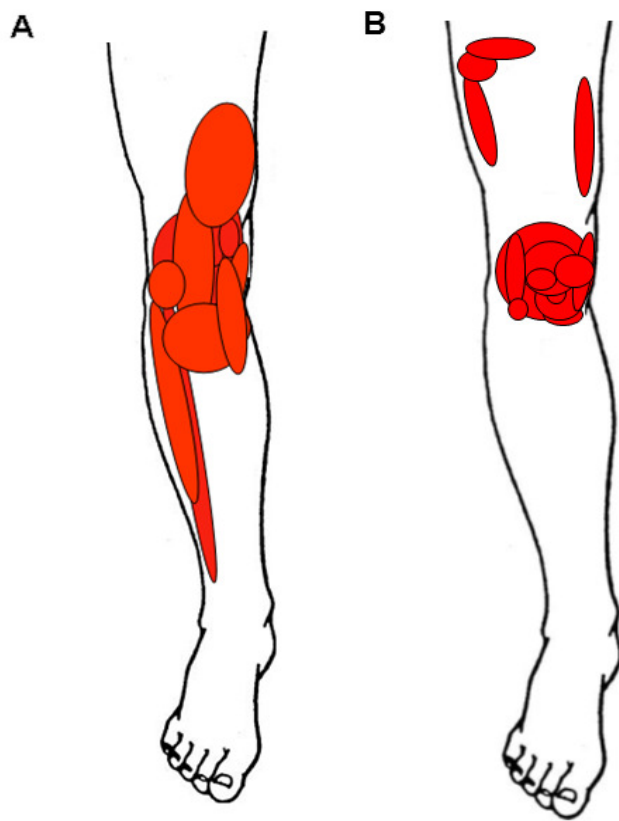


Figure 11 Illustrating pain distribution after injection of hypertonic saline in patients with knee OA (A; study iii) and healthy subjects (B; study i)

Pain description

When describing the experimental pain in the present thesis, the healthy subjects in study (i) and individuals with knee OA in study (iii) used similar words (Table 1).

Subclasses	Before (knee OA)	After (knee OA)	After (healthy)
<i>Sensory descriptors:</i> Throbbing Shooting Drilling Sharp Tugging Wrenching Burning Smarting Dull Sore Hurting Aching Taut	N=3 N=3 N=3 N=3 N=3 N=3	 N=3 N=4 N=4 N=4	 N=3 N=4 N=4 N=3 N=4
<i>Affective descriptors:</i> Tiring Cruel	N=3	N=4 N=3	N=3
<i>Evaluative descriptors:</i> Annoying Miserable Intense	N=3		N=3 N=3 N=4
<i>Miscellaneous descriptors:</i> Penetrating Piercing Tight		N=6	N=3 N=4 N=4

Table 1: Words describing the quality of pain before (before knee OA), and after induction of hypertonic saline in patients with knee OA (after knee OA) and in healthy subjects (after healthy). Words used ≥ 3 times by the participants has been included in the table (knee OA; study iii and healthy; study i).

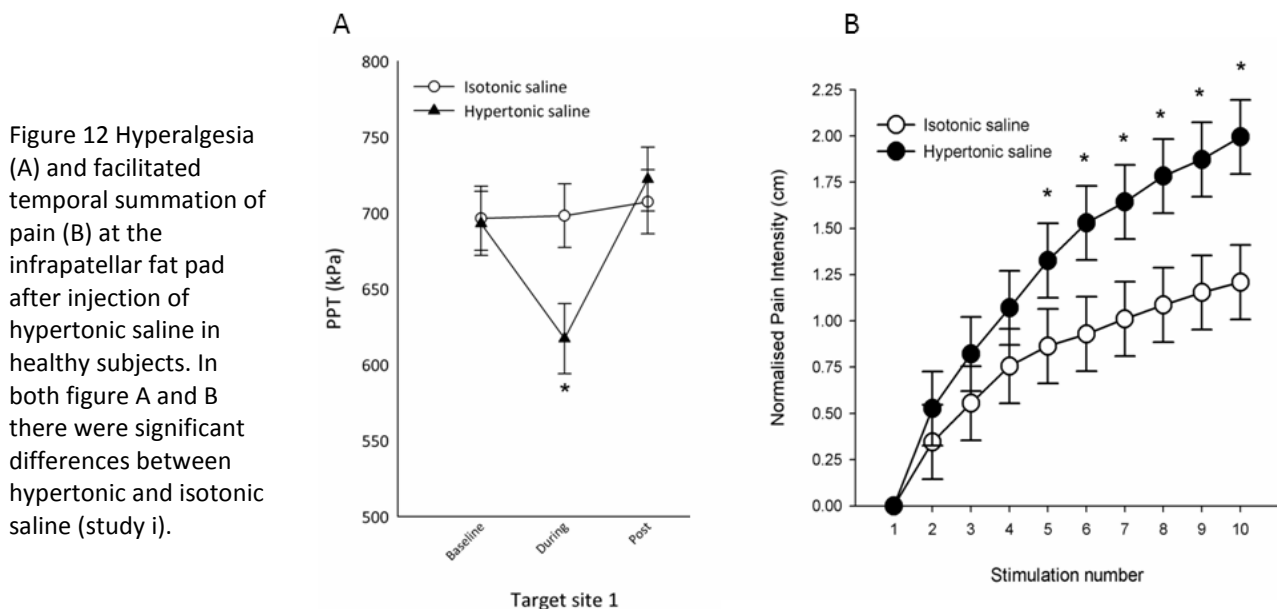
Cumulative data suggest that people with OA can experience pain caused by both nociceptive and neuropathic mechanisms to varying degrees [128;129]. The likely neuropathic mechanism in OA is central sensitisation, which may arise from chronic nociceptor stimulation and subsequent modification of central pain-transmitting neurons [130].

A recent focus group study on the hip/knee OA pain experience identified that participants used a broad range of descriptors to characterise their pain [131] which is in line with the present study (iii). A focus group study by Hochman et al. [113] found that 34% of knee OA participants used pain quality descriptions suggestive of neuropathic pain. Neuropathic mechanisms may therefore contribute to the pain experience of a subset of adults with chronic, symptomatic knee OA. The use of both neuropathic and nociceptive descriptors by some of the individuals suggests that OA can be associated with a mixture of pain mechanisms [113]. This might be part of the reason why the healthy subjects and the individuals with knee OA used different words to describe the experimental pain.

Experimental knee pain and healthy subjects

Experimental approaches using healthy subjects provide a unique opportunity to study the pain pattern arising from nociceptive stimulation of specific structures without any influences from other conditions related to knee pathology (e.g. inflammation, co-morbidities, central sensitisation etc.).

In study (i) the experimental knee pain model showed that hyperalgesia and facilitated temporal summation of pressure pain were found at the knee (figure 12; A&B) and knee-related muscles.



The increased sensitivity was exclusive to deep tissue, and no changes in decreased pain sensitivity were found for either cutaneous or contralateral pain sensitivity. The hyperalgesia induced by experimental knee pain in study (i) has also been identified in different tissues induced by different analgesic substances in healthy subjects [54;79;95-99]. The pain induced by hypertonic saline occurs immediately and is not associated with tissue damage or toxicity [132]; thus no inflammatory reactions in the tissue are present.

In addition, the findings in study (i) show that pain from normal tissue, without interference from inflammation, can elicit facilitation of central mechanisms in healthy subjects, as facilitated temporal summation of pressure pain in the infrapatellar fat pad and in muscles located distant to the actual experimental pain site was observed. These results indicate enhanced sensitivity of the central mechanisms responsible for temporal summation of pain. In line with study (i), previous studies have reported mechanically stimulated facilitated temporal summation of pain in muscles in healthy subjects after induction of experimental pain [77;133;134].

In patients with knee OA facilitated temporal summation was found in both the same segment and the neighbouring segment and at the contralateral site [64]. This is in contrast with the findings in study (i), as we did not find facilitated temporal summation at the contralateral leg. The discrepancies between the two studies might be caused by the fact that facilitated central mechanisms in neighbouring segments seen in knee OA patients occur over time [13] and by the fact that the excitation and sensitisation of nociceptors, due to tissue damage, might cause sufficient nociceptive input to the central pain systems to initiate central sensitisation.

Experimental knee pain and knee OA

Earlier studies have suggested that knee OA patients generally have higher pain sensitivity compared to controls [62;63;119] indicating defects in central pain processing.

Local hyperalgesia (Figure 13A) to pressure stimulation during experimental knee pain (as compared with the control injection) in clinical pain-relief treated patients with knee OA was observed in study (iii), in line with those observed in healthy subjects [63;126] and in individuals with knee OA [62] suggesting facilitated pain mechanisms.

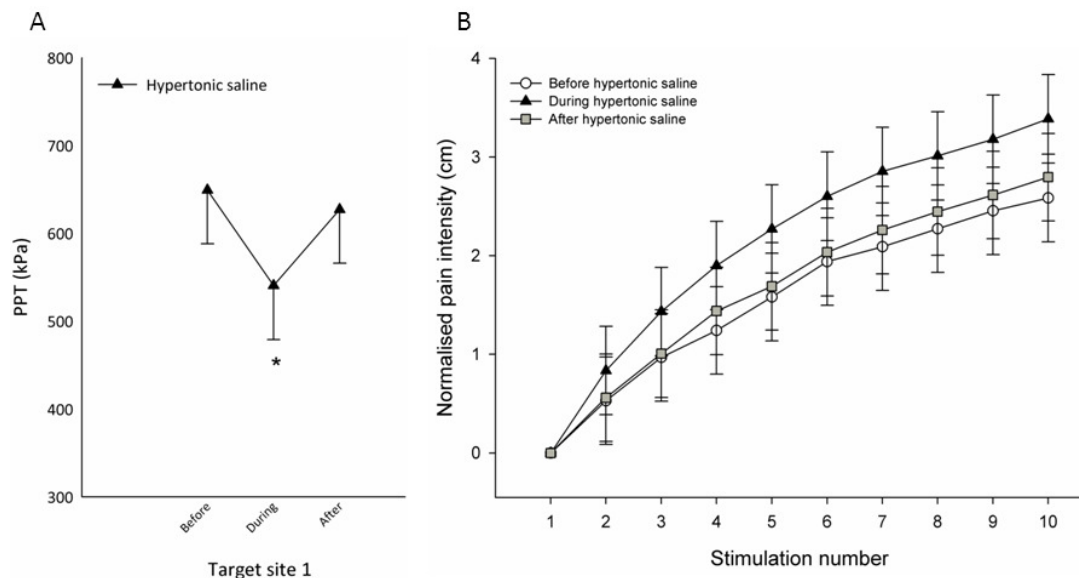


Figure 13 Hyperalgesia (A) and facilitated temporal summation of pain (B) at the infrapatellar fat pad after injection of hypertonic saline in patients with knee OA (study iii).

These findings corroborate findings by Rakel et al. [63] , where hyperalgesia to pressure stimulation was observed at the affected knee but not at distant sites, but in contrast to studies measuring PPTs in participants with advanced knee OA pain showing significantly lower PPTs at the effected knee and also at distant sites compared to controls [15;64]. The reason for this discrepancy could be related to the severity of the pain which was mild in the present study

The experimental knee pain in study (iii) also facilitated temporal summation of pressure pain (as compared to the control injection) at the knee (Figure 13B) and adjacent muscles located proximally and distally to the actual experimental pain site, which is in line with observations previously seen in clinical studies [64;86;135;136] and among the healthy subjects in study (i) This indicates an enhanced sensitivity of the central mechanisms responsible for temporal summation of pain.

The results in study (iii) indicate that the dynamics (i.e., the adaptive responses to pain) of the nociceptive system is intact among individuals with knee OA, as the responses to experimental pain are similar to those previously observed from healthy subjects, showing that the pain system in individuals with knee OA can be affected even after many years of nociceptive input. The rekindled hyperalgesia caused by the experimental pain model indicates that the sensitisation is latent despite the effect of the pain-reducing treatment, which is suggestive of more persistent plastic changes in the central nervous system with chronic pain.

No previous studies have shown the enhanced pain sensitivity mechanisms in painful but otherwise healthy knees reported in study (i), indicating that the infrapatellar fat pad pain may contribute significantly to hyperalgesia and sensitisation phenomena and offer a potential mechanism in individuals with knee OA. Furthermore, it has been suggested that knee OA pain

may result from mild inflammation in structures such as synovial layers [11], and the infrapatellar fat pad may also be involved [108].

In summary

Acute experimental knee pain induced in healthy subjects and individuals with knee OA leads to hyperalgesia and facilitated temporal summation in the knee and surrounding muscles. This was regardless of whether the individuals with knee OA had received pain-reducing treatment before the induced experimental pain.

The present thesis illustrates that the dynamics of the nociceptive system (i.e., the adaptive responses to pain) was intact in individuals with chronic knee OA pain, as the responses to experimental pain are similar to those previously observed among healthy subjects, showing that the pain system in individuals with knee OA can be affected even after many years of nociceptive input. The experimental knee pain model used in this thesis may be valuable for assessing the effects of pain modulation of both local and facilitated central mechanisms related to knee OA.

Limitations

Important limitations to the present thesis are the short-lasting and highly-controlled experimental pain stimulus in study (i), which provides a different pain experience than the chronic pain condition of individuals with knee OA. Nevertheless, the experimental approach offers the translation from fundamental mechanisms to clinical implications. The lack of a control group in study (ii) is another limitation of this thesis. Thus, placebo effects in study (ii) cannot be ruled out, and placebo might explain the immediate increase in PPT at the control site post-

injection. Furthermore, it has been shown that intra-articular local anesthetic have analgesic effects for up to 7 days [114], which may confound our findings somewhat. Lack of power (small sample size) in studies (ii) and (iii) may have precluded detection of statistically significant associations. However, these data are the first of their kind and constitute important stepping stones for future investigations.

The weaknesses of the design were compensated for by adding an extra baseline test to assess measurement stability and regression to the mean phenomena before intervening in study (ii). Intra-session analyses were conducted to explore a possible significant difference between the two baseline tests in all the analyses, and no significant differences were found (data not shown). Also, the results were robust across multiple methods, assessing pain sensitivity locally and regionally, and with different methods of pressure application (computer-controlled vs. manual). This adds strength to the current findings despite the small sample size and uncontrolled study design.

Concluding remarks

The present work has showed that experimental knee joint pain leads to hyperalgesia and facilitated temporal summation of pain, not only in the infrapatellar fat pad, but also in muscles located distant to the injection site, in subjects with no history of knee pain. The changes observed suggest involvement of both local and widespread hyperalgesia and sensitisation of facilitated pain mechanisms similar to those observed among knee OA patients, indicating that the infrapatellar fat pad pain may contribute significantly to the sensitisation phenomena seen in knee OA patients.

The results reported in the present work indicate that the intra-articular analgesia in patients with knee OA lead to reduced pain sensitivity at the knee and surrounding muscles, and this effect was sustained and even augmented by the anti-inflammatory treatment of intra-articular glucocorticosteroid, as shown by assessment of the effects 2 weeks after injection. No significant changes in pain sensitivity were observed at the control site on the contralateral arm, suggesting that local and widespread hyperalgesia is regulated by nociceptive input from the joint periphery.

Reducing knee OA pain with intra-articular analgesia and anti-inflammatory treatment reduced the degree of knee hyperalgesia. These results might support the notion that inflammation may play an important role in sensitisation of the nociceptive system in both joint and soft tissues in knee OA. Experimental knee pain induced in the infrapatellar fat pad in the same patient evoked local and widespread hyperalgesia in the infrapatellar fat pad and in muscles located distant to the injection site as seen in healthy subjects. This illustrates that the dynamics of the nociceptive system (i.e., the adaptive responses to pain) was intact in individuals with chronic knee OA pain, as the responses to experimental pain are similar to those previously observed among healthy subjects, showing that the pain system in individuals with knee OA can be affected even after many years of nociceptive input. The experimental knee pain model might be valuable for assessing the effects of pain modulation of both local and widespread pain mechanisms related to knee OA.

Although knee OA is a chronic pain condition associated with increased pain sensitivity, this thesis indicates that the adaptability of the pain system is intact, making it possible to prevent the development of centralised pain syndromes. The novel results of the studies illustrate the dynamics of the nociceptive system in individuals with knee OA, which might contribute to a

better understanding and development of more rational therapies of the central pain mechanisms, when targeting pain relief in individuals with knee OA.

Perspectives

Despite the high prevalence of knee OA it remains one of the most frequent knee disorders without a cure. Pain and disability are prominent clinical features of knee OA. Therefore, pain therapy is an important medical need which is rarely met. Still, many patients undergo surgical joint replacement after many years of pain. Thus, it is very important to improve our knowledge of pain generation in knee OA, with the hope of finding better treatment strategies.

Summary

Pain is the cardinal symptom of knee osteoarthritis (OA), and currently this disease cannot be cured. Pain and disability are prominent clinical features of knee OA.

Some of the mechanisms underlying the pain are unknown. To optimally treat this common disease, an understanding of the causes of pain is needed. Especially, knowledge of how joint pain affects the pain systems will provide important new insight and help to explain the basic pain mechanisms in humans.

The acute experimental knee pain induced in healthy subjects in study (i) and individuals with knee OA in study (iii) leads to hyperalgesia and facilitated temporal summation in the knee and surrounding muscles, regardless of whether the individuals with knee OA had received pain-reducing treatment before the induced experimental pain. This indicates that the dynamics of the nociceptive system (i.e., the adaptive responses to pain) was intact in individuals with chronic knee OA pain, as the responses to experimental pain are similar to those previously observed among healthy subjects, showing that the pain system in individuals with knee OA can be affected even after many years of nociceptive input. The experimental knee pain model used in this thesis may be valuable for assessing the effects of pain modulation of both local and facilitated central mechanisms related to knee OA.

Hyperalgesia and facilitated central pain mechanisms observed in individuals with knee OA were reduced after injection of intra-articular analgesia and anti-inflammatory treatment in both the knee and surrounding muscles (ii). The effects were immediate and were sustained for at least 2 weeks. This supports the notion that inflammation may play an important role in the sensitisation of the nociceptive system in both joint and soft tissues in individuals with knee OA.

The novel results of this thesis might contribute to a better understanding and development of more rational therapies of the central pain mechanisms, when targeting pain relief in individuals with knee OA.

Summary in Danish (Dansk resumé)

Knæ smerter er blandt de hyppigste muskuloskeletale smerter, den hyppigste årsag til nedsat funktionsniveau og et kardinalsymptom ved knæ-artrose (knæ-OA). Nociception er den fysiologiske mekanisme, som omfatter alle neurale processer til bearbejdning af vævsskadelige påvirkninger, hvilket vil sige eksitation af bl.a. smertereceptorer. Smerte er et resultat af den nociceptive aktivering af fremmende og hæmmende systemers modaliteter, og hvordan den justeres ved bl.a. knæ-OA er endnu ikke helt klarlagt.

Smarter ved knæ-OA kan være forårsaget af perifer og central sensibilisering af smertesystemerne, som resulterer i, at normale stimuli opleves som smertefulde. Formålet med afhandlingen er at belyse nogle af de mekanismer, der ligger til grund for knæ smerter. Mere viden er nødvendig for at forstå disse smerteproblemer. Specielt kræves større viden om, hvilke mekanismer der aktiveres ved dybe smerter. En sådan viden vil være værdifuld ved såvel smertebehandling som øvrige behandlinger af personer med knæ-OA.

Smertesystemets reaktion på eksperimentel smerte induceret i fedtpuden lige under knæet i studie (i) medførte reduceret smertefølsomhed i knæet og de omkringliggende muskler hos raske forsøgspersoner. Denne er sammenlignelig med smertefølsomheden observeret hos personer med slidgigt i knæet. Disse resultater indikerer, at fedtpuden muligvis spiller en vigtig rolle i forbindelse med smertefølsomheden hos personer med knæ-OA.

Intra-artikulær injektion af smertelindrende behandling til personer med knæ-OA i studie (iii) førte til væsentlig smertelindring i knæet og de omkringliggende muskler i op til 2 uger efter injektionen. Disse resultater tyder på, at betændelse i knæet kan spille en vigtig rolle i forhold til sensitisering af smertesystemet hos personer med knæ-OA.

Eksperimentel smerte påført de samme personer med slidgigt i knæet, som i studie (ii) havde modtaget en effektiv lindrende smertebehandling af deres knæ smerter, medførte både lokal (ved knæet) og udbredt (ved de omkringliggende muskler) forværring af smertefølsomheden (iii).

Selvom knæ-OA er en kronisk smertetilstand associeret med øget smertefølsomhed (øget smerteoplevelse), indikerer resultaterne af afhandlingen, at smertesystemets tilpasningsevne er intakt, hvilket åbner op for muligheden for at udvikle behandlingsstrategier til personer med knæ-OA, der forhindrer udviklingen af central sensitisering.

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